An Urgent Need for Local Guidelines to Address Phosphate Homeostasis in Children with Transfusion-dependent β-thalassemia Major

Sir,

The purpose of this communication is to alert the readers and other relevant stakeholders about a significant problem of a need of local guidelines on the management of metabolic bone disease (MBD) in children with β-thalassemia major (β-TM).

MBDs of multifactorial origin are frequently encountered in the children with β-TM. With a carrier frequency of 6-7% of β-thalassemia gene in the Pakistani population, around 5, 250 infants are born with β-TM annually. Yet, there is no national interest to address bone disorders in these patients. In the last decade, areas of vitamin D, calcium (Ca), and PTH homeostasis in patients with transfusion-dependent β-TM have been researched extensively. However, the effects on phosphate (PO_4) homeostasis are unclear.

Results from our unpublished pilot study revealed that 36.5% (n=134) of transfusion-dependent β-TM children (n=380; age range 5-17 years) had high-serum PO_4 levels (Median= 6.13 mg/dl with IQR of 7-5.7), findings consistent with the study by Tangngam *et al.*, which found asymptomatic hypoparathyroidism in 38% of the β-TM patients.[1] These patients also had significantly lower median plasma fibroblast growth factor-23 (FGF-23) levels than controls.[1] More studies on metabolic bone disease in children with β-TM by the Research Group at our institute show significant growth failure secondary to the iron overload with high-serum ferritin levels, denoting ineffective chelation.[2] High prevalence of bone pains and fragility fractures was significantly associated with hypovitaminosis D, hypocalcaemia, and hyperphosphatemia.[3] Sultan *et al.* reported altered biochemical markers of bone turnover in regularly transfused thalassemic patients, highlighting a direct correlation between serum PO_4 and ferritin levels. Both hypo- and hyperphosphatemia were seen in the patients.[4] Similarly, in the population studied by Mirhosseini *et al.*, a high prevalence of hypocalcaemia (22%) and hyperphosphatemia (41.7%) suggested the incidence of asymptomatic hypoparathyroidism in patients with β-TM.[5]

Iron overload in β-TM contributes to low-circulating FGF-23 levels, leading to the high PO_4 loading. Physiologically, serum PO_4 is regulated by PTH, vitamin D, FGF-23, and its cofactor Klotho. FGF-23 reduces the formation of 1, 25-(OH)2 D by inhibiting 1 alpha-hydroxylase, and as findings suggest, its impaired response may disrupt PO_4 homeostasis that is furthering a vicious cycle of bone disease. We urge researchers to explore the relation among iron overload, FGF-23, and the Ca-PO_4-PTH axis, so that we can develop local guidelines on the nutritional and pharmacological management of MBD in children with β-TM, which will help in lessening the economic burden of this life-altering disease.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
LJ, AHK: Idea conception, letter revision, and review.
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